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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,532	02/09/2001	Clive Wood	GNN-012CP	8383

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Ivor R. Elrifi
MINTZ LEVIN COHEN COHN FERRIS GLOVSKY AND POPEO PC
One Financial Center
Boston, MA 02111

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/780,532	WOOD ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-8 and 39-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-8 and 39-65* is/are rejected.

7)☒ Claim(s) *2,3,5-8 and 39-50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/19/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 3, 5-8, 39-65 are pending in the application.

This Office Action is in response to the Amendment filed on 11/12/03.

Response to Amendment

Claims 2, 3, 5-8 and newly added claims 39-65 stand rejected under 35 U.S.C. 112 1st paragraph (written description) for reasons set forth of the record mailed on 11/19/02 and further discussed below.

Claims 2, 3, 5-8, 39-65 are rejected under 35 U.S.C. 112 2nd paragraph for reasons set forth of the record mailed on 11/19/02 and further discussed below.

Claims 2, 3, 5-8 and 39-65 are objected to for reasons discussed below.

Claims 2, 3, 5-8, 39-65 are rejected under 35 U.S.C. 112 1st paragraph (enablement) for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 5-8 and newly added claims 39-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to this rejection, Applicants argue that claim 2 has been amended to specify that the recited polypeptide is defined by specific structural and functional features. In addition, the polypeptide used to modulate cell proliferation must be at least 80% identical to amino acid 1-168 of SEQ ID NO:2 and inhibit the activity of a TRADEα polypeptide. Applicants thus conclude that the claims satisfy the written description requirement.

The above arguments have been fully considered but deemed unpersuasive. Contrary to Applicant's assertion, the polypeptide recited in claim 2 is not limited to a specific structural and functional features. The claim recites a TRADEα polypeptide comprising a TRADEα polypeptide sequence a least 90% identical to SEQ ID NO:2. This potentially encompasses a large genus of polypeptides of various length as long as it contains a segment of sequence that is 90% identical to SEQ ID NO:2, and such polypeptide(s) has the function of modulate NFkB signaling pathway. The specification only discloses that two TNF receptors, TRADEα and TRADEβ, which is able to activate NFkB dependent transcription. As discussed in the previous office action, the written description requires the invention is described by a representative species by their complete structure or other identifying characteristics. As such, the specification fails to describe a representative number of TRADEα polypeptides that have different lengths which comprise a sequence 90% to SEQ ID NO:2, and such polypeptides have the function of modulating NFkB signaling pathway. Therefore, the written description requirement is not met.

The claimed genus of "a polypeptide agent" also fails to meet the written description requirement. Contrary to Applicant's assertion, not all claims recite the "80% identical to amino acid 1-168 of SEQ ID NO:2" limitation (Claims 2, 3, 5-8, 39-41, 46-52). The "polypeptide agent" thus encompasses potentially a large genus of polypeptides of different sizes, classes or

origins that have the ability of modulating NFkB signaling pathway. As discussed above, the specification only discloses that two TNF receptors, TRADEα and TRADEβ, which is able to activate NFkB dependent transcription. Moreover, even the claims recite "the polypeptide agent is a soluble form of a TRADEα polypeptide comprising a mature TRADEα polypeptide extracellular domain", "a TRADEα-Fc fusion protein", "the polypeptide agent is a TRADEα polypeptide sequence comprising 80% identical to amino acid 1-168 of SEQ ID NO:2," "the polypeptide agent is a TRADEα polypeptide sequence comprising 90% identical to amino acid 1-168 of SEQ ID NO:2," "the polypeptide agent is a TRADEα polypeptide sequence comprising amino acid 1-168 of SEQ ID NO:2," or "the polypeptide agent is a TRADEα polypeptide sequence comprising at least one of the domains corresponding to amino acid 29-63 of SEQ ID NO:2, amino acid 72-114 of SEQ ID NO:2, amino acids 114-139 of SEQ ID NO:2, or amino acids 137-168 of SEQ ID NO:2," fails to meet the written description requirement. Such recitations all encompass a potentially large genus of polypeptides of different sizes, classes and origins as long as they contain a segment of sequence that shares certain percentage of sequence similarities to SEQ ID NO:2. The specification fails to teach a representative number of such polypeptides have NFkB modulating function. Therefore, the written description requirement is not met.

Claim 53 recites "a TRADEα polypeptide sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complement of nucleotides 1-504 of SEQ ID NO:1, wherein said polypeptide inhibits the activity of TRADEα." Such recitation encompasses a potentially large genus of unrelated polynucleotides of different size. The specification fails to

disclose any such polynucleotides that inhibit the activity of TRADEα. The structural functional relationship does not exist. Therefore, the written description requirement is not met.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 5-8 and 39-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to this response, Applicants argue that the amended claims are directed to a specific polypeptide sequence. The claims are thus definite.

This argument has been fully considered but deemed unpersuasive. The amended claims still recite "a TRADEα" and "a TRADEβ" polypeptide. The recitation of "a TRADEα" or "a TRADEβ" polypeptide renders the claims indefinite because it is unclear which polypeptide applicants are referring to. According to the specification, there is only one TRADEα and one TRADEβ. The use of "a" implies there is more than one such polypeptide. As such, the metes and bounds of the claims cannot be established. Therefore, this rejection is maintained.

New Grounds of Rejection Necessitated by Applicant's Amendment

Election/Restrictions

Applicant's election without traverse of inventions comprise SEQ ID NO:2 in the response filed on 11/12/03 is acknowledged.

Claim Objections

Claims 2, 3, 5-8 and 39-65 are objected to for containing non-elected subject matter. Applicants elected claims directed to SEQ ID NO: 2 only. Amending the claims such that they are only directed to elected inventions is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 5-8, 39-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention

The claims are drawn to a method for modulating activation of an NFkB signaling pathway in a cell comprising contacting cell with a polypeptide that modulates the activity of a TRADEα polypeptide that comprising a sequence sharing 90% of sequence similarity with SEQ ID NO: 2, or a TRADEβ polypeptide sequence 90% identical to SEQ ID NO: 4, thereby a NFkB signaling pathway is modulated. The claims are further drawn to such a method, wherein the polypeptide agent is limited to a fusion of TRADEα-Fc, comprising extracellular domain of TRADEα, or comprising a polypeptide encoded by a nucleic acid hybridizes under stringent condition to the nucleic acid encoding the extracellular domain of TRADEα.

The breadth of the claim

The broadest claim (2) is drawn to a method of modulating activation of an NFkB signaling pathway in a cell by any type of polypeptide that modulates the activity of a TRADEα polypeptide comprising a sequence sharing 90% of sequence similarity with SEQ ID NO: 2, or a TRADEβ polypeptide sequence 90% identical to SEQ ID NO: 4. The claims also encompasses such a method, wherein the polypeptide agent can either activates or inhibits the NFkB signaling.

The teaching of the specification and working examples

The specification teaches that the TRADEα polypeptide represented by the sequence of SEQ ID NO:2, and the TRADEβ represented by the sequence of SEQ ID NO:4 activate the NFkB mediated transcription in cells co-transfected with TRADEα or β and reporter constructs comprising promoter with NFkB element. The specification further demonstrates through deletion mutants of TRADEα or β that it is the intracellular domain (169-417 of SEQ ID NO:2) of the TRADEα or β, rather than the extracellular domain (1-168 of SEQ ID NO:2), involves in

such activation. The specification fails to teach any fusions proteins of either TRADE polypeptide, polypeptides comprising extracellular domain of TRADE, or polypeptides comprising a segment that shares 90% sequence similarity to the extracellular domain can activate or inhibit NFkB signaling pathway. In fact, the specification fails to teach any polypeptide agent that inhibits NFkB signaling through modulation of TRADEα molecule. The specification also fails to provide any working example in this regard. Moreover, the specification fails to teach how to use the claimed method.

The state of art and the level of predictability

The state of art at the time of filing teaches that the TNF receptor superfamily comprising a number receptor including Apo4, αOAF065, TRAIN receptor. The prior art also teaches that these receptor share sequence similarities at certain region. However, the prior art does not teach a TRADE molecule that belongs to this superfamily. Moreover, the prior art is silent on the function of the TRADE molecule to modulate NFkB signaling pathway. Therefore, the enablement of the claimed invention relies solely on the teaching of specification.

As discussed above, the teaching of the specification is limited in view of the claimed scope. In addition, the specification also fails to teach how to use this method. The specification teaches that TRADE modulating agents can be used as prophylactics or therapeutic agents to treat diseases. However, there is no known disease result from expression of non-expression of TRADE identified at present. The specification fails to teach any disease result from TRADE dis-regulation. In addition, the specification fails to teach the nexus between the claimed method, the modulation of NFkB, and the modulation of TRADE itself. The specification thus fails to provide a patentable use for the claimed method. As such, one of skilled in the art would

have to engage in undue experimentation to make or use the invention. Therefore, the claimed invention is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 5-8 and 39-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 2, 3, 5-8 and 39-52, the recitation of "a polypeptide agent that modulates the activity of a TRADEα polypeptide comprising a TRADEα polypeptide..." renders the claims indefinite because it is unclear which polypeptide applicants are referring to. In other words, does the "polypeptide agent" comprise a TRADEα polypeptide sequence at least 90% identical to SEQ ID NO:2, or the "TRADEα polypeptide" comprising such polypeptide? Clarification is required.

Regarding claims 6-8, 39-41, the word "mature" renders the claims indefinite because the specification does not disclose what is a mature TRADEα extracellular domain. Without such disclosure, it is unclear how one can distinguish said mature TRADEα extracellular domain from an immature one.

Regarding claims 53-65, the recitation of "said polypeptide agent inhibits the activity of a TRADEα polypeptide sequence" renders the claims indefinite because it is unclear how the activity of a polypeptide sequence can be inhibited. Although a polypeptide may have activity, the polypeptide sequence does not have any activity that can be inhibited by a polypeptide agent.

Regarding claims 59-62, the recitation of "soluble form of the TRADEα polypeptide sequence is a TRADEα-Fc fusion protein" renders the claim indefinite because it is unclear how a polypeptide sequence can be a fusion protein. A fusion protein is a molecule, which is not a sequence itself.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER